

REMARKS

Upon entry of the instant amendment, claims 1 and 7-19 will be pending in the above-identified application and stand ready for further action on the merits.

In this Amendment, claims 1 and 15 have been amended without prejudice or disclaimer of the subject matter contained therein. New claims 16-19 have been added. Support for amended claims 1 and 15 and new claims 16-19 can be found at least at page 12, lines 1-22, and Examples 1-6 of the present Specification. No new matter has been introduced by way of the instant Amendment.

Examiner Interview

Examiner Chang is thanked for extending Applicants' representative the courtesy of an interview on February 4, 2010, to discuss proposed amendments to the claims, additional data, and distinctions over the cited art. The Examiner's Interview Summary resulting from the interview correctly states the substance of the interview, attendees, etc.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Claims 1 and 15 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the phrase "in a reaction solvent of toluene in which appropriate quantities of soluble solvent is added" is said to introduce new matter.

Applicants have amended claims 1 and 15 to delete reference to "appropriate quantities" and to better define the composition of the reaction solvent, in order to obviate this rejection. As pointed out above, support for the amendments to claims 1 and 15 can be found at least at page

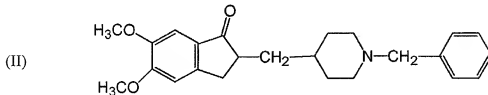
12, lines 1-22, and Examples 1-6 of the present Specification. As discussed below, the volume ratios for volume reaction solvent to amount of compound having structural formula (III) in Examples 1-6 of the present application are 8:1, 7:1, 8:1, 7:1, 8:1, and 7:1, respectively. Further support for such amendments at pages 9-10 and 13 of the Specification was pointed out by the Examiner at pages 2 and 3 of the Office Action. Thus, in view of the discussion above, Applicants respectfully request that the rejection of claims 1 and 15 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Claims 1 and 7-15 are rejected under 35 U.S.C. § 103(a) over JP-A-179151 (*hereinafter referred to as D1*)(supplemented with the corresponding patent US 4,898,841) or JP-61-187674 (*hereinafter referred to as D3*)(supplemented with its English Abstract CA118).

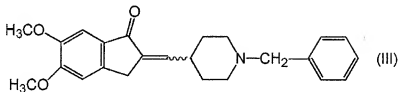
D1 and D3 taken alone or together do not teach a process with a Raney nickel catalyst in a reaction solvent of tetrahydrofuran, toluene, or a solvent mixture of toluene and an alcohol with a volume ratio of between 7:1 (7 times) and 10:1 (10 times) for reaction solvent to a compound having structural formula (III).

D1 and D3 taken alone or together do not teach a process for preparing a compound of the structural formula (II):



in the presence of a Raney nickel catalyst in a reaction solvent of tetrahydrofuran, toluene, or a

solvent mixture of toluene and an alcohol, wherein the reaction solvent is 7 to 10 times the volume of the compound of the structural formula (III)



as in the claimed invention.

As previously pointed out by the Examiner, **DI** does not disclose any specific catalytic reaction processes using a Raney nickel catalyst, although Example 4 teaches production of a compound of structural formula II using a catalytic reduction with a palladium-carbon catalyst. (Example 1 teaches production of a compound having a structure similar to that of formula II with a rhodium-carbon catalyst.) Thus, **DI** does not teach a volume ratio of between 7:1 (7 times) and 10:1 (10 times) for volume reaction solvent to amount of compound having structural formula (III), as in the claimed invention.

Example 4 of **DI** discloses reacting 0.4 g of a compound of the structural formula (III) in 16 ml of reaction solvent (*e.g.*, methylene chloride:methanol), and thus the approximate volume ratio in Example 4 is 40:1 (40 times). Example 1 of **DI** does not teach a compound of the structural formula (III) or the product of the claimed invention, however it has a volume ratio of reaction solvent to reactant of 27:1.

Volume ratios for reaction solvent to a compound having structural formula (III) taught by *D1* and *D3* are much higher than those of the claimed invention, although the product yields are similar to those of the claimed invention.

The volume ratios for Examples 1 and 4 of *D1* are much higher than those of the claimed invention, which are between 7:1 and 10:1. (The volume ratios for volume reaction solvent to amount of compound having structural formula (III) in Examples 1-6 of the present application are 8:1, 7:1, 8:1, 7:1, 8:1, and 7:1, respectively.) Furthermore, the product yields of Examples 1-6 (82.8%, 76.6%, 80%, 74.9%, 81.5%, and 94.6%, respectively) of the present application and that for Example 4 (82%) of *D1* are comparable. (Again, the product of Example 1 of *D1* is not the same as that of the claimed invention.) This is important, because a smaller volume of reaction solvent is used and then removed in the claimed process for a given amount of product, as compared to the volume of reaction solvent used and then removed for the specific catalytic reduction process taught by *D1*. As stated above, *D1* does not teach or suggest the volume ratio range of reaction solvent to compound of the structural formula (III) recited in the pending claims.

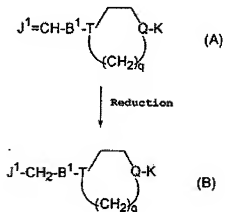
D3 does not teach a Raney nickel catalyst as in the claimed invention. As previously pointed out by the Examiner in the Office Action mailed March 24, 2009, *D3* discloses the use of ruthenium catalysts. Still further the volume ratio of reaction solvent to the reactant (e.g., compound of the structural formula (III)) in all of the examples of *D3* is 15:1, which is outside the range of the claimed invention, while the yields (85.4%-87%) are also similar to those of Examples 1-6 of the present application.

Thus, as with *D1* above, a smaller volume of reaction solvent is used and then removed in the claimed process for a given amount of product, as compared to the volume of reaction

Thus, taken alone or together **D1** and **D3** do not teach each and every element of the claimed invention, as they do not teach the volume ratio range for reaction solvent to compound of the structural formula (III) of between 7:1 and 10:1. Applicants respectfully request that the rejection of claims 1 and 7-15 under 35 U.S.C. § 103(a) be withdrawn.

It would not have been obvious to one of ordinary skill in the art at the time the invention

In addition, while *DI* teaches the generic reduction reaction



may be carried out using “a catalyst such as a catalyst of palladium and carbon, Raney nickel and a catalyst of rhodium and carbon” (US 4,495,841, col. 21, line 68 to col. 22, line 3), it does not specify which reaction solvents should be used with particular catalysts and reactants. Examples

1 and 4 of *DI*, discussed above, both use tetrahydrofuran (THF) as a reaction solvent, but neither example uses a Raney nickel catalyst and Example 1 does not produced the claimed product.

One of skill in the art at the time the claimed invention was made would be aware of the technical difficulties associated with using a Raney nickel catalyst in a reaction solvent of THF, toluene, or a solvent mixture of toluene and an alcohol. It is well known in the art that a Raney nickel catalyst will spontaneously ignite if it becomes dry. (**See attached MSDSs for Raney nickel catalyst labeled Exhibits 1 and 2.**)

Therefore, at the time the invention was made there were serious concerns about the safety of using a Raney nickel catalyst in THF, toluene, or a solvent mixture of toluene and an alcohol in large-scale industrial production methods. In fact, when Applicants tried to engage a company that specializes in catalytic reduction processes to perform the claimed methods, the company declined citing the combination of Raney nickel catalyst and THF as being too dangerous (due to concerns that flammable THF might be ignited by dried Raney nickel catalyst). It is common knowledge in the art that Raney nickel catalyst should be preserved in water or alcohol, because it is likely to ignite spontaneously when it dries. For this reason Raney nickel catalyst is usually used with an alcohol.

Thus, although Raney nickel catalysts are used in the selective reduction of olefins and *DI* separately discloses Raney nickel catalyst as one possible catalyst and THF as a reaction solvent with other catalysts, one of ordinary skill in the art at the time the invention was made would not have been motivated to combine a Raney nickel catalyst with THF, toluene, or a solvent mixture of toluene and an alcohol, as suggested by the Examiner. Instead one of skill in

the art would have been motivated to select an alcohol as a reaction solvent with a Raney nickel catalyst.

This assertion is further supported by two references cited in the International Search Report, CHEN, X. *Asymmetry*, 2002, Vol. 13, No. 1, pp. 43-46 and OGAWARA, "Gosei Shiyaku," 1980, Kodansha Ltd., page 313, which disclose the use of a Raney nickel catalyst with ethanol for reduction reactions, but not THF, toluene, or a solvent mixture of toluene and an alcohol, as in the claimed invention. In view of the safety concerns associated with Raney nickel catalysts, one of ordinary skill in the art at the time the invention was made would have been motivated to choose a catalyst (such as a palladium catalyst) that is more manageable in industrial processes.

Furthermore, the ratio volume of reaction solvent to compound of the structural formula (III) in the claimed invention is even more non-obvious, as the claimed combination of reactant (*e.g.*, compound of the structural formula (III)), reaction solvent (*e.g.*, compound of the structural formula (III)) and Raney nickel catalyst by itself would not have been obvious to one of skill in the art at the time the claimed invention was made.

As explained above, Raney nickel catalyst can spontaneously ignite when it becomes dry. Thus, for safety reasons, it is important to ensure that Raney nickel catalyst is stored in liquid. In fact, Raney nickel catalyst is sold as slurry in water and/or alcohol. The claimed methods use relatively smaller volumes of reaction solvent to produce the compound of the structural formula (II) than methods disclosed by the cited art. One of ordinary skill in the art would not have been motivated to use smaller reaction solvent volumes with a Raney nickel catalyst than those used with other catalysts in the cited art, because of safety concerns. By decreasing the volume of

reaction solvent, one of skill in the art would expect the risk of unintentionally permitting the Raney nickel catalyst to dry and ignite to be increased (especially in a manufacturing environment where flammable solvents like THF are present).

The purity of donepezil produced by the unobvious combination of a Raney nickel catalyst and THF, toluene, or a solvent mixture of toluene and an alcohol, with a volume ratio of reaction solvent to compound of structural formula (III) of between 7:1 and 10:1 is unexpected.

The claimed methods permit production of high-purity donepezil that can be obtained without purification steps being necessary after the reduction reaction. The donepezil produced by the claimed methods (including a Raney nickel catalyst and THF, toluene, or a solvent mixture of toluene and an alcohol) can be used directly in preparing its hydrochloride salt without intervening purification steps. This added benefit of using the Raney nickel catalyst with compound of the structural formula (III) and THF, toluene, or a solvent mixture of toluene and an alcohol in the volume ratios recited in the claims would not have been obvious to one of skill in the art at the time the invention was made based on the cited art.

Data taken from Table 1 on page 18 of the Specification is reproduced below for the Examiner's convenience. Example 1 in Table 1 shows that the purity of a hydrogenated reaction solution (free donepezil) is as high as 99.6%, and that of the final product is 99.8%. Thus, additional purification (such as crystallization) after the reductive reaction has little effect. The degree of purity of free donepezil produced using the claimed methods would not have been obvious to one of skill in the art at the time the invention was made.

Examples 1-6 represent working examples of the claimed invention and produce free donepezil of higher purity than Examples 7-9, which employ alcohol and/or ethyl acetate reaction solvents, not the THF, toluene, or a solvent mixture of toluene and an alcohol, as recited

in the claims. Furthermore, reference Examples 1-3, which combine THF with rhodium-carbon or palladium-carbon catalysts produce free donepezil having a much lower degree of purity than Examples 1-6, which are directed to the claimed invention.

In Example 6 of the present Specification, the reaction product was not crystallized before being reacted with hydrochloric acid to produce donepezil hydrochloride. Thus, high purity donepezil hydrochloride can be prepared without column chromatography or isolation of the initial reduction reaction product by crystallization as is common with other catalyst systems.

The degree of product purity achieved is due to the unexpected selectivity of the Raney nickel catalyst when used with THF, toluene, or a solvent mixture of toluene and an alcohol with the volume ratios of reaction solvent to reactant recited in the claims.

Table 1

Test Sample	Hydrogenated Reaction Solution Purity (%)
Example 1	99.6
Example 2	99.0
Example 3	99.1
Example 4	99.4
Example 5	99.1
Example 6	99.0
Example 7	96.5
Example 8	95.8
Example 9	97.8
Reference	85.8
Reference	91.5
Reference	75.2

As Applicants have previously explained, the degree of purity indicated in Table 1 for products of the claimed methods is higher than the degree of purity achieved by methods taught in *D3*, for example, while the product yields remain similar. Thus, the claimed process is more efficient than those taught by the cited art.

To further support this position, Applicants have attached a report (**Exhibit 3**) entitled “**Donepezil reaction mixture HPLC results of Commercial batches (384 kg scale)**.” The data is for the years 2007-2009, and the reactions were conducted with a Raney nickel catalyst in THF, where the volume of THF relative to the volume of the compound of the structural formula (III) was about 7:1 or 8:1, as in the claims. As the data shows, the average purity of free donepezil was 99.849% with a standard deviation of 0.010. The purity of the product produced by the claimed methods is very consistent. Furthermore, the amount of undesirable debenzylated byproduct produced is very low, when compared to processes described in the cited art. It is unexpected that during production of donepezil on a large-scale (384 kg) that such a high degree of selectivity/purity could be achieved by using a Raney nickel catalyst and THF with the volume ratio of reaction solvent and reactant recited in the claims.

In view of the discussion above, Applicants respectfully request that the rejection of claims 1 and 7-15 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Based upon the amendments and remarks presented herein, the Examiner is respectfully requested to issue a Notice of Allowance clearly indicating that each of the pending claims 1 and 7-19 is allowable under the provisions of Title 35 of the United States Code.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Stephanie A. Wardwell, Ph.D., Reg. No. 48,025 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: February 5, 2010

Respectfully submitted,

By 

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Enclosures: Two MSDSs for Raney nickel catalyst (Exhibits 1 and 2) (total 8 pages)
Donepezil reaction mixture HPLC results of Commercial batches (384 kg scale)
(Exhibit 3) (2 pages)

Safety data for Nickel



Glossary of terms on this data sheet.

The information on this web page is provided to help you to work safely, but it is intended to be an overview of hazards, not a replacement for a full Material Safety Data Sheet (MSDS). MSDS forms can be downloaded from the web sites of many chemical suppliers.

General

Synonyms: alcan 756, carbonyl nickel powder, C.I. 77775, EL12, fibrex, fibrex P, NI 270, nickel 2170, nickel sponge, nickel catalyst, NI 0901-s, NI 4303T, NP2, Raney alloy, Raney nickel

Molecular formula: Ni

CAS No: 7440-02-0

EC No: 231-111-4

EC Index No: 028-002-00-7

Physical data

Appearance: silver white, hard, malleable metal chunks or grey powder

Melting point: 1453 C

Boiling point: 2732 C

Vapour density:

Vapour pressure:

Specific gravity: 8.9

Flash point:

Explosion limits:

Autoignition temperature:

Stability

Stable in massive form. Powder is pyrophoric - can ignite spontaneously. May react violently with titanium, ammonium nitrate, potassium perchlorate, hydrazoic acid. Incompatible with acids, oxidizing agents, sulfur.

Toxicology

Carcinogen. Toxic by all routes of entry. May cause sensitization by skin contact. Typical TLV 0.05 mg/m³

Toxicity data

(The meaning of any toxicological abbreviations which appear in this section is given [here](#).)

IPR-RAT LD50 250 mg kg⁻¹

Risk phrases

(The meaning of any risk phrases which appear in this section is given [here](#).)

R10 R17 R36 R37 R38 R40 R42 R43.

Transport information

(The meaning of any UN hazard codes which appear in this section is given [here](#).)

UN No 3089. Packing group II. Hazard class 4.1.

Personal protection

Good ventilation. Wear gloves and safety glasses when handling the powder.

Safety phrases

(The meaning of any safety phrases which appear in this section is given [here](#).)

S16 S22 S26 S36.

[Return to [Physical & Theoretical Chemistry Lab. Safety home page](#).]

This information was last updated on October 27, 2004. We have tried to make it as accurate and useful as possible, but can take no responsibility for its use, misuse, or accuracy. We have not verified this information, and cannot guarantee that it is up-to-date.

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MATERIAL SAFETY DATA SHEET

Date Printed: 02/03/2010

Date Updated: 10/29/2009

Version 1.7

Section 1 - Product and Company Information

Product Name	RANEY 2800 NICKEL, ACTIVE CATALYST, SLURRY IN WATER
Product Number	221678
Brand	ALDRICH
Company	Sigma-Aldrich
Address	3050 Spruce Street SAINT LOUIS MO 63103 US
Technical Phone:	800-325-5832
Fax:	800-325-5052
Emergency Phone:	314-776-6555

Section 2 - Composition/Information on Ingredient

Substance Name	CAS #	SARA 313
ACTIVATED NICKEL CATALYST, IN WATER	None	Yes

Ingredient Name	CAS #	Percent	SARA 313
RANEY NICKEL	7440-02-0		Yes
WATER	7732-18-5		No

Formula Ni

Section 3 - Hazards Identification

EMERGENCY OVERVIEW

Toxic. Flammable (USA) Highly Flammable (EU).
May cause sensitization by inhalation and skin contact. Toxic by
inhalation, in contact with skin and if swallowed. May cause
cancer. Irritating to eyes, respiratory system and skin.
Spontaneously flammable in air.
Target organ(s): Nose. Lungs.

HMIS RATING

HEALTH: 3*
FLAMMABILITY: 3
REACTIVITY: 0

NFPA RATING

HEALTH: 3
FLAMMABILITY: 3
REACTIVITY: 0

*additional chronic hazards present.

For additional information on toxicity, please refer to Section 11.

Section 4 - First Aid Measures

ORAL EXPOSURE

If swallowed, wash out mouth with water provided person is

conscious. Call a physician.

INHALATION EXPOSURE

If inhaled, remove to fresh air. If not breathing give artificial respiration. If breathing is difficult, give oxygen.

DERMAL EXPOSURE

In case of contact, immediately wash skin with soap and copious amounts of water.

EYE EXPOSURE

In case of contact, immediately flush eyes with copious amounts of water for at least 15 minutes.

Section 5 - Fire Fighting Measures

FLAMMABLE HAZARDS

Flammable Hazards: Yes

EXPLOSION HAZARDS

Vapor may travel considerable distance to source of ignition and flash back. Container explosion may occur under fire conditions.

CONDITIONS OF FLAMMABILITY

Dry active Raney nickel is pyrophoric. If allowed to dry in air, it may smolder to red heat and provide a combustion source for exposed combustible materials.

FLASH POINT

N/A

AUTOIGNITION TEMP

N/A

FLAMMABILITY

N/A

EXTINGUISHING MEDIA

Suitable: For small (incipient) fires, use media such as "alcohol" foam, dry chemical, or carbon dioxide. For large fires, apply water from as far as possible. Use very large quantities (flooding) of water applied as a mist or spray; solid streams of water may be ineffective. Cool all affected containers with flooding quantities of water.

FIREFIGHTING

Protective Equipment: Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes. Specific Hazard(s): Flammable liquid. Emits toxic fumes under fire conditions.

Section 6 - Accidental Release Measures

PROCEDURE TO BE FOLLOWED IN CASE OF LEAK OR SPILL

Evacuate area. Shut off all sources of ignition.

PROCEDURE(S) OF PERSONAL PRECAUTION(S)

Wear respirator, chemical safety goggles, rubber boots, and heavy rubber gloves.

METHODS FOR CLEANING UP

Cover with dry-lime, sand, or soda ash. Place in covered

containers using non-sparking tools and transport outdoors. Ventilate area and wash spill site after material pickup is complete.

Section 7 - Handling and Storage

HANDLING

User Exposure: Avoid breathing vapor. Avoid contact with eyes, skin, and clothing. Avoid prolonged or repeated exposure.

STORAGE

Suitable: Keep container closed. Keep away from heat, sparks, and open flame.

Section 8 - Exposure Controls / PPE

ENGINEERING CONTROLS

Safety shower and eye bath. Use nonsparking tools. Mechanical exhaust required.

PERSONAL PROTECTIVE EQUIPMENT

Respiratory: Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU). Where risk assessment shows air-purifying respirators are appropriate use a full-face respirator with multi-purpose combination (US) or type ABEK (EN 14387) respirator cartridges as a backup to engineering controls. If the respirator is the sole means of protection, use a full-face supplied air respirator.
Hand: Compatible chemical-resistant gloves.
Eye: Chemical safety goggles.

GENERAL HYGIENE MEASURES

Wash thoroughly after handling. Wash contaminated clothing before reuse.

Section 9 - Physical/Chemical Properties

Appearance	Physical State: Liquid Color: Grey Form: Suspension	
Property	Value	At Temperature or Pressure
Molecular Weight	58.69 AMU	
pH	9.0 - 11.0	20 °C
BP/BP Range	N/A	
MP/MP Range	N/A	
Freezing Point	N/A	
Vapor Pressure	N/A	
Vapor Density	N/A	
Saturated Vapor Conc.	N/A	
Bulk Density	N/A	
Odor Threshold	N/A	
Volatile%	N/A	
VOC Content	N/A	
Water Content	N/A	
Solvent Content	N/A	
Evaporation Rate	N/A	
Viscosity	N/A	
Surface Tension	N/A	
Partition Coefficient	N/A	
Decomposition Temp.	N/A	

Flash Point	N/A
Explosion Limits	N/A
Flammability	N/A
Autoignition Temp	N/A
Refractive Index	N/A
Optical Rotation	N/A
Miscellaneous Data	N/A
Solubility	N/A

N/A = not available

Section 10 - Stability and Reactivity

STABILITY

Stable: Stable.

Conditions of Instability: Highly reactive with organic compounds when heated or allowed to dry.

Materials to Avoid: Strong acids, Strong oxidizing agents, Sulfur Nickel may react violently with titanium, ammonium nitrate, potassium perchlorate, and hydrazoic acid.

HAZARDOUS DECOMPOSITION PRODUCTS

Hazardous Decomposition Products: Toxic metal oxides will be formed by exposure to air.

HAZARDOUS POLYMERIZATION

Hazardous Polymerization: Will not occur

Section 11 - Toxicological Information

ROUTE OF EXPOSURE

Skin Contact: Causes skin irritation.

Skin Absorption: May be harmful if absorbed through the skin.

Eye Contact: Causes eye irritation.

Inhalation: May be harmful if inhaled. Material is irritating to mucous membranes and upper respiratory tract.

Ingestion: May be harmful if swallowed.

SENSITIZATION

Skin: May cause allergic skin reaction.

TARGET ORGAN(S) OR SYSTEM(S)

Cardiovascular system. Blood. G.I. System. Liver. Nose. Lungs.

SIGNS AND SYMPTOMS OF EXPOSURE

To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

CHRONIC EXPOSURE - CARCINOGEN

Result: This product is or contains a component that has been reported to be possibly carcinogenic based on its IARC, ACGIH, NTP, or EPA classification.

Section 12 - Ecological Information

No data available.

Section 13 - Disposal Considerations

APPROPRIATE METHOD OF DISPOSAL OF SUBSTANCE OR PREPARATION

Catalyst should be deactivated with bleach solution before disposal. Contact a licensed professional waste disposal service

to dispose of this material. Observe all federal, state, and local environmental regulations.

Section 14 - Transport Information

DOT

Proper Shipping Name: Metal catalyst, wetted [with a visible excess of liquid]
UN#: 1378
Class: 4.2
Packing Group: Packing Group II
Hazard Label: Spontaneously combustible
PIH: Not PIH

IATA

Proper Shipping Name: Metal catalyst, wetted
IATA UN Number: 1378
Hazard Class: 4.2
Packing Group: II
Not Allowed - Aircraft: Cargo aircraft only. Not permitted on passenger aircraft.

Section 15 - Regulatory Information

EU ADDITIONAL CLASSIFICATION

Symbol of Danger: F-Xn
Indication of Danger: Highly Flammable. Harmful.
R: 17-40-43
Risk Statements: Spontaneously flammable in air. Limited evidence of a carcinogenic effect. May cause sensitization by skin contact.
S: 5-15-22-36
Safety Statements: Keep contents under water. Keep away from heat. Do not breathe dust. Wear suitable protective clothing.

US CLASSIFICATION AND LABEL TEXT

Indication of Danger: Toxic. Flammable (USA) Highly Flammable (EU).
Risk Statements: May cause sensitization by inhalation and skin contact. Toxic by inhalation, in contact with skin and if swallowed. May cause cancer. Irritating to eyes, respiratory system and skin. Spontaneously flammable in air.
Safety Statements: Keep container tightly closed in a cool well-ventilated place. Keep away from sources of ignition - no smoking. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable protective clothing, gloves, and eye/face protection.
US Statements: Target organ(s): Nose. Lungs.

UNITED STATES REGULATORY INFORMATION

SARA LISTED: Yes
DEMINIMIS: 0.1 %
NOTES: This product is subject to SARA section 313 reporting requirements.

CANADA REGULATORY INFORMATION

WHMIS Classification: This product has been classified in accordance with the hazard criteria of the CPR, and the MSDS contains all the information required by the CPR.
DSL: No
NDSL: No

DISCLAIMER

For R&D use only. Not for drug, household or other uses.

WARRANTY

The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Inc., shall not be held liable for any damage resulting from handling or from contact with the above product. See reverse side of invoice or packing slip for additional terms and conditions of sale. Copyright 2009 Sigma-Aldrich Co. License granted to make unlimited paper copies for internal use only.

Donepezil reaction mixture HPLC results of Commercial batches (384kg scale)
2007-2009

2010/1/13



Analysis date	Lot No.	Relative peak area (%)	
		Debenzylated Compound	Donepezil
2007.05.17	17051301	0.12	99.83
2007.05.21	17051701	0.11	99.86
2007.05.25	17052102	0.10	99.85
2007.05.29	17052501	0.11	99.84
2007.06.02	17052902	0.13	99.84
2007.06.04	17053101	0.11	99.84
2007.06.06	17060201	0.11	99.84
2007.06.08	17060403	0.10	99.84
2007.06.10	17060602	0.11	99.84
2007.06.12	17060801	0.10	99.85
2007.06.14	17061001	0.11	99.82
2007.06.22	17061203	0.10	99.85
2007.06.24	17061402	0.10	99.84
2007.06.26	17062201	0.11	99.84
2007.06.28	17062401	0.10	99.85
2007.06.30	17062601	0.12	99.85
2007.07.02	17062801	0.10	99.85
2007.07.04	17063001	0.10	99.85
2007.07.06	17070201	0.10	99.85
2007.07.08	17070401	0.10	99.85
2007.07.10	17070601	0.10	99.85
2007.07.12	17070801	0.10	99.84
2007.07.14	17071001	0.10	99.85
2007.07.16	17071201	0.10	99.86
2007.07.18	17071401	0.11	99.85
2007.07.20	17071602	0.10	99.85
2007.07.24	17072003	0.10	99.85
2007.07.22	17071803	0.11	99.84
2007.09.07	17090304	0.10	99.86
2007.09.09	17090502	0.09	99.85
2007.09.11	17090701	0.10	99.86
2007.09.13	17090901	0.13	99.86
2007.09.15	17091103	0.12	99.85
2007.09.17	17091301	0.11	99.84
2007.09.21	17091704	0.09	99.86
2007.09.23	17091902	0.11	99.85
2007.09.25	17092101	0.10	99.85

(Continued)

Analysis date	Lot No.	Relative peak area (%)	
		Debenzylated Compound	Donepezil
2008.04.08	18040202	0.11	99.85
2008.04.10	18040601	0.11	99.86
2008.04.14	18041002	0.11	99.85
2008.04.16	18041201	0.12	99.85
2008.04.18	18041403	0.13	99.84
2008.04.20	18041602	0.12	99.82
2008.05.18	18042201	0.11	99.85
2008.05.20	18051604	0.12	99.84
2008.05.22	18051801	0.11	99.85
2008.05.24	18052001	0.11	99.85
2008.05.26	18052202	0.11	99.85
2008.05.28	18052401	0.10	99.86
2008.05.30	18052603	0.13	99.83
2008.06.01	18052802	0.12	99.84
2009.05.19	19051102	0.11	99.85
2009.05.23	19051501	0.09	99.86
2009.05.27	19052301	0.09	99.88
2009.05.31	19052701	0.10	99.86
2009.06.04	19053101	0.11	99.86
2009.06.08	19060402	0.10	99.86
2009.06.12	19060802	0.10	99.86
2009.06.16	19061201	0.10	99.86
2009.06.20	19061601	0.12	99.85
2009.06.24	19062001	0.10	99.86
2009.06.28	19062402	0.11	99.86
2009.07.02	19062801	0.11	99.85
2009.07.06	19070201	0.10	99.86
2009.07.08	19070401	0.12	99.84
2009.07.10	19070601	0.09	99.86
	Average	0.107	99.849
	s	0.010	0.010
	Ave.+3s	0.137	99.880
	Ave.-3s	0.077	99.819

s: Standard Deviation